REMARKS

Claims 44-57 and 62-68 were pending in this application. Claims 44, 45, 50, 51, and 66 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in the present application and/or one or more related applications. Claims 46-49, 52-57, 62, 64, and 65 have been amended to clarify the invention. Support for the amendments to claims 46-49, 52-57, 62, 64, and 65 can be found in the specification at, *e.g.* page 5, paragraph [0018], page 10, paragraph [0030], page 14, paragraph [0040], page 53, paragraph [0124] and page 108, paragraph [292]. Thus, no new matter has been added. After entry of the present Amendment, claims 46-49, 52-57, and 62-68 will be pending.

CLAIM INTERPRETATION

The Examiner states that the term "with specificity" is being interpreted as broadly as possible in light of the specification (*see* Final Office Action dated February 4, 2011 ("Final Office Action"), page 2, last paragraph). Applicants respectfully point out that the term "with specificity" is not present in the claims of the instant application. In fact, the term "specifically" was deleted from the claims, in the response to the Office Action mailed January 13, 2010, that was filed July 13, 2010. Accordingly, Applicants submit that the issue of claim interpretation is moot.

THE REJECTION UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claims 44, 50-52, 54-56, 64 and 65 are rejected under 35 U.S.C. § 102(b) as allegedly being unpatentable over Claffey *et al.*, 1998, Mol. Cell. Biol., 9: 469-481 ("Claffey"). Applicants respectfully disagree with the rejection for the reasons detailed below.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987).

Claffey fails to anticipate claims the claims because Claffey does not teach each and every element of the claims. Specifically, Claffey does not teach a method for identifying a compound that modulates human vascular endothelial growth factor (VEGF) mRNA

translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with a human cell engineered to express a reporter protein translated from an mRNA transcript comprising a reporter gene coding sequence operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the reporter gene coding sequence is not the coding sequence of human VEGF. Claffey is focused on examining the effect of hypoxia on human VEGF mRNA transcription and the role of the 3' UTR of VEGF in mediating this effect (*see* Abstract). Claffey examines the role of the 3' UTR in VEGF mRNA transcription under hypoxic conditions by using luciferase-VEGF cDNA constructs comprising VEGF cDNA sequences that comprise the full-length 3' UTR of the VEGF gene inserted between the luciferase gene and the polyadenylation site (*see* Claffey, p. 476, Col. 1, 1st paragraph to Col. 2, 1st paragraph and Figure 7). In fact, the entire VEGF 5'UTR sequence and coding region was deleted from the cDNA sequences used in the luciferase-VEGF cDNA constructs of Claffey (see Claffey, p. 471, col. 1, 1st paragraph). The luciferase-VEGF mRNA constructs of Claffey do not comprise the full-length 5' UTR of human VEGF, as required by the claims. In addition, Applicants respectfully point out that Figure 3B of Claffey does not depict a reporter gene construct, but rather a schematic map of a complete VPF/$VEGF_{165}$ cDNA that contains the open reading frame of VEGF, in contrast to the rejected claims. Thus, not every element of the pending claims is taught by Claffey.

In view of the foregoing, Applicants submit that Claffey does not anticipate the pending claims, and respectfully request that this rejection be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

1. The Rejection over Claffey in view of Levy

Claims 45, 50-52 and 54-57 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Claffey as applied to claims 44, 50-52, 54-56, 64 and 65, and further in view of Levy *et al.*, 1998, J. Biol. Chem. 273(11): 6417-6423 ("Levy"). Applicants respectfully disagree with the rejection for the reasons detailed below.

Consistent with the principles enunciated in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), a *prima facie* case of obviousness can only be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference and to carry out the modification with a reasonable expectation of success, viewed in light of the prior art.

For the reasons discussed above, nowhere does Claffey teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with either a cell engineered to express a reporter protein translated from a mRNA transcript or a composition comprising a cell-free translation mixture and a RNA transcript expressing a reporter protein translated from the RNA transcript, wherein the mRNA transcript comprises a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the 5' UTR is upstream of the reporter gene coding sequence and the 3' UTR is downstream of the reporter gene coding sequence, and wherein the reporter gene coding sequence is not the coding sequence of human VEGF. Moreover, since Claffey is only focused on examining the importance of the 3' UTR of human VEGF in increasing VEGF transcription and mRNA stability in response to hypoxia, Claffey provides no suggestion or reason to one of ordinary skill in the art to modify the luciferase-VEGF cDNA constructs of Claffey to include the full-length human VEGF 5' UTR, as required by the claims.

Furthermore, nowhere does Claffey teach or suggest a screening assay that involves contacting the compound with a second human cell engineered to express a second reporter protein translated from a second mRNA transcript or a second composition comprising a second cell-free extract and a second mRNA transcript, comprising the first reporter gene coding sequence operably linked to a second 5' UTR and a second 3' UTR, wherein the second 5' UTR is upstream of the first reporter gene coding sequence and the second 3' UTR is downstream of the first reporter gene coding sequence, and wherein the second 5' UTR and the second 3' UTR are each from a mRNA different than the 5' UTR and the 3' UTR of the human VEGF mRNA. There is nothing taught in Claffey that would have prompted a person of ordinary skill in the art to develop methods for screening for candidate compounds that that modulates human VEGF mRNA translation that is regulated by the UTRs of the human

VEGF mRNA, wherein the methods comprise contacting the compound with either a second host cell engineered to express a second reporter protein translated from a second mRNA transcript or a second composition comprising a second cell-free extract and a second mRNA transcript comprising the 3' UTR and the 5' UTR of a *different* mRNA, as required by the claims, with a reasonable expectation of success.

Levy does not cure the deficiencies of Claffey. Levy is a study aimed at determining whether the 36-kDa RNA binding protein, HuR, is involved in hypoxic stabilization of VEGF (*see* Levy Abstract). Levy describes *in vitro* binding experiments that show that the HuR protein binds with high affinity and specificity to a 45 nucleotide fragment within the VRS (the VEGF regulatory segment) of the 3' UTR of VEGF to regulate VEGF mRNA stability under hypoxic conditions (*see* Levy, page 6419, Col. 1 to Col. 2). Levy also describes actinomycin D chase experiments that comparatively show that antisense-mediated inhibition of HuR expression blocked hypoxic stabilization of VEGF mRNA (*see* Levy at page 6419, 2nd Col., last paragraph to page 6420, 2nd Col., 2nd paragraph) while the overexpression of HuR increased VEGF mRNA stability under hypoxic conditions (*see* Levy at page 6420, Col. 2, 3rd paragraph to page 6421, Col. 2, 1st paragraph). Levy further describes an *in vitro* RNA degradation assay using capped, polyadenylated VEGF 3' UTR transcripts and S-100 cytoplasmic extracts to show that the addition of exogenous HuR stabilized VEGF mRNA significantly (*see* Levy at page 6421, Col. 2, 2nd paragraph). Levy compares VEGF mRNA stabilization by the HuR protein under normoxic and hypoxic conditions but nowhere does Levy teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with either a cell engineered to express a reporter protein translated from a mRNA transcript or a composition comprising a cell-free translation mixture and a RNA transcript expressing a reporter protein translated from the RNA transcript, wherein the mRNA transcript comprises a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the 5' UTR is upstream of the reporter gene coding sequence and the 3' UTR is downstream of the reporter gene coding sequence, and wherein the reporter gene coding sequence is not the coding sequence of human VEGF. There is no hint or suggestion in Levy of any type of reporter assay, let alone one that involves cells or cell-extracts

containing the reporter mRNA transcripts used in the claimed methods. As such, Levy does not cure the deficiencies of Claffey.

Furthermore, nowhere does Levy teach or suggest a screening assay that involves contacting the compound with a second human cell engineered to express a second reporter protein translated from a second mRNA transcript or a second composition comprising a second cell-free extract and a second mRNA transcript, comprising the first reporter gene coding sequence operably linked to a second 5' UTR and a second 3' UTR, wherein the second 5' UTR is upstream of the first reporter gene coding sequence and the second 3' UTR is downstream of the first reporter gene coding sequence, and wherein the second 5' UTR and the second 3' UTR are each from a mRNA different than the 5' UTR and the 3' UTR of the human VEGF mRNA. There is nothing taught in Levy that would have prompted a person of ordinary skill in the art to develop methods for screening for candidate compounds that that modulates human VEGF mRNA translation that is regulated by the UTRs of the human VEGF mRNA, wherein the methods comprise contacting the compound with either a second host cell engineered to express a second reporter protein translated from a second mRNA transcript or a second composition comprising a second cell-free extract and a second mRNA transcript, wherein the second mRNA transcript comprises the 3' UTR and the 5' UTR of a *different* mRNA, as required by the claims, with a reasonable expectation of success.

Further, even if the teachings of Claffey and Levy were combined, the combined teachings would not result in the screening assays of the claimed invention. The combined teachings of Claffey and Levy would, at most, have suggested assessing whether HuR binds to the 3' UTR of VEGF and whether HuR plays a role in regulating the stability of VEGF mRNA in response to hypoxia, by using the assays described in Claffey and conducting the assays in cell-free extracts under normoxic and hypoxic conditions as described in Claffey and Levy. Accordingly, Levy, whether alone or in combination with Claffey, does not render obvious the claims.

In view of the foregoing, Applicants submit that the pending claims are patentable over Claffey as applied to claims 44, 50-52, 54-56, 64 and 65, and further in view of Levy, and respectfully request that this rejection be withdrawn.

2. **The Rejection over Claffey in view of Stein**

Claims 46 and 47 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Claffey as applied to claims 44, 50-52, 54-56, 64 and 65, and further in view of Stein *et al.*, 1998, Mol. Cell. Biol. 18(6): 3112-63119 ("Stein"). Applicants respectfully disagree with the rejection of claims 46 and 47 for the reasons detailed below.

Applicants respectfully submit that claims 46 and 47 are patentable over Claffey because, as discussed in detail above, Claffey does not teach or suggest the methods of claims 46 and 47.

Stein does not cure the deficiencies of Claffey. The Examiner states that "[w]ith regard to claim 46-47, Stein teaches (b) contacting a compound with a panel of human cells, wherein each human cell in the panel is isolated from each other and each human cell is engineered to express a reporter protein translated from a reporter mRNA operably linked to a 5' UTR and a 3' UTR of a mRNA other than the human VEGF mRNA (p. 3115, Figure 3, where the reporter was operably linked to UTR of BiP mRNA instead of VEGF)" (*see* Final Office Action at page 11, the first paragraph). Applicants respectfully submit that the Examiner has erroneously characterized the teaching of Stein. Stein describes reporter assays performed under normoxic and hypoxic conditions using monocistronic and bicistronic reporter gene constructs in order to confirm that the murine 5' UTR of VEGF contains a functional IRES (*see* Stein at page 3114, Col. 2, last paragraph to page 3115, Col. 1, 1st paragraph and Figure 5 caption). Stein performs the reporter assays under normoxic and hypoxic conditions using monocistronic and bicistronic reporter gene constructs in order to compare the relative strength of the IRES in the 5' UTR of murine VEGF to the IRES in BiP (*see* Stein at page 3115, Col. 1, last paragraph to Col. 2, 1st paragraph). The monocistronic and bicistronic reporter constructs of Stein contain either: (i) the 5' UTR of murine VEGF linked to SeAP, (ii) a mutant of the 5' UTR of murine VEGF linked to SeAP, or (iii) the 5' UTR of BiP linked to SeAP. None of the constructs described in Stein contain both the full-length 5' UTR and full-length 3' UTR of human VEGF (*see* Stein at page 3114, Col. 2, last paragraph to page 3115, Col. 2, 1st paragraph and page 3113, Fig. 1 description). Furthermore, the cells used to perform the reporter assays in Stein were never contacted with a compound, but rather were exposed to normoxic or hypoxic conditions, wherein hypoxic conditions are characterized by a reduction in oxygen available to the cells, under which IRES-induced reporter expression was determined. Thus, Stein would not have taught or suggested to a person of ordinary skill in the art a method for identifying a compound that

modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, comprising contacting a compound with a human cell engineered to express a reporter protein translated from a mRNA transcript comprising a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR, wherein the 5' UTR is upstream of the reporter gene coding sequence and the 3' UTR is downstream of the reporter gene coding sequence and, wherein the reporter gene coding sequence is not the coding sequence of human VEGF mRNA, as required by claims 46 and 47. Moreover, nowhere does Stein teach or suggest contacting the compound with human cells in a plurality of wells, wherein each well contains human cells engineered to express a reporter protein translated from a mRNA transcript comprising the first reporter gene coding sequence operably linked to a 5' UTR and a 3' UTR, wherein the 5' UTR is upstream of the first reporter gene coding sequence and the 3' UTR is downstream of the first reporter gene coding sequence; and, wherein the 5' UTR and the 3' UTR are each from a mRNA different than the 5' UTR and the 3' UTR of the human VEGF mRNA as required in claim 47. As such, Stein does not cure the deficiencies of Claffey.

Further, even if the teachings of Claffey and Stein were combined, the combined teachings would not result in the screening assays of the claimed invention. Accordingly, Stein, whether alone or in combination with Claffey, does not render obvious claims 46 and 47.

In view of the foregoing, Applicants submit that claims 46 and 47 are patentable over Claffey, as applied to claims 44, 50-52, 54-56, 64 and 65, and further in view of Stein, and respectfully request that this rejection be withdrawn.

3. The Rejection over Claffey in view of Levy and Stein

Claim 48 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Claffey in view of Levy, as applied to claims 46 and 47, and further in view of Stein. Applicants respectfully disagree with the rejection of claim 48 for the reasons detailed below.

Independent claim 48 is patentable over Claffey, Levy and Stein because for the reasons discussed above neither Claffey, Levy nor Stein teach or suggest, or provide any reason that would have prompted a person of ordinary skill in the art to perform a screening assay for identifying compounds that modulate human VEGF mRNA translation that is

regulated by the untranslated regions of human VEGF mRNA, by performing reporter assays using reporter mRNA transcripts that comprise both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA. Moreover, there is no teaching or suggestion in Claffey, Levy or Stein of contacting a compound with a first mRNA transcript comprising a first reporter gene coding sequence, operably linked to the first full-length 5' UTR and the first full-length 3' UTR of the human VEGF, wherein the first reporter gene coding sequence is not the coding sequence of human VEGF mRNA; and contacting the compound with a second mRNA transcript comprising the first reporter gene coding sequence, operably linked to a second 5' UTR and a second 3' UTR different than the 5' UTR and the 3' UTR of the human VEGF mRNA, as required by claim 48, for the reasons discussed above.

Furthermore, Applicants respectfully submit that the teaching of Stein does not scientifically support the Examiner's argument that "one of ordinary skill in the art...would have adjusted the teachings of Claffey and Levy to include...an additional control, including the 5' and 3' UTR regulatory regions from a different gene as taught by Stein." (*see* the Final Office Action at page 14, 2nd paragraph). Stein describes cell-based reporter assays to determine whether the 5' UTR of the murine VEGF mRNA has an IRES which provides IRES-induced translation, and the relative strength of the IRES in either the VEGF or BiP mRNA. To make such determinations, Stein uses bicistronic reporter gene constructs containing either: (i) the 5' UTR of murine VEGF linked to SeAP, (ii) a mutant of the 5' UTR of murine VEGF linked to SeAP, or (iii) the 5' UTR of BiP linked to SeAP. One of ordinary skill in the art would have recognized that such bicistronic reporter gene constructs are used in cell-based assays to specifically test a mRNA sequence for the presence of an IRES or whether the mRNA has IRES-inducible activity. Thus, the Examiner's allegation of the obviousness of claim 48 based on the combined teachings of Claffey and Levy in view of Stein would not have made scientific sense to one of ordinary skill in the art, even if hindsight were inappropriately applied.

The combined teachings of Claffey, Levy, and Stein would, at most, have suggested assessing the role of the 3' UTR in mediating VEGF transcription and mRNA stability in response to hypoxia by using the assays described in Claffey, and assessing whether the 5' UTR of VEGF contains functional IRES elements by using the assays described in Stein, while conducting these experiments in cell-free extracts, under normoxic and hypoxic

conditions. Accordingly, Stein, whether alone or in combination with Claffey and Levy, does not render obvious claim 48.

In view of the foregoing, Applicants submit that claim 48 is patentable over Claffey in view of Levy, as applied to claims 46 and 47, and further in view of Stein, and respectfully request that this rejection be withdrawn.

4. The Rejection over Claffey in view of Benjamin

Claim 53 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Claffey, as applied to claims 44, 50-52, 54-56, 58, 59, 64 and 65, and further in view of Benjamin *et al.*, 1997, PNAS, 94: 8761-8766 ("Benjamin"). Applicants respectfully disagree with the rejection of claim 53 for the reasons detailed below.

As discussed above, nowhere does Claffey teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with a human cell engineered to express a reporter protein translated from an mRNA transcript comprising a reporter gene coding sequence operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the reporter gene coding sequence is not the coding sequence of VEGF, such as recited in claim 44. Moreover, since Claffey is only focused on examining the importance of the 3' UTR of human VEGF in increasing VEGF transcription and mRNA stability in response to hypoxia, Claffey provides no suggestion or reason to one of ordinary skill in the art to modify the luciferase-VEGF cDNA constructs of Claffey to include full-length human VEGF 5' UTR, as required by the claims.

Benjamin does not cure the deficiencies of Claffey. Benjamin describes a tetracycline-regulated VEGF expression system in glioma cell xenografts (*see* Benjamin at p. 8761, Col. 2, 2nd paragraph). In order to develop the system, cells were transfected with a construct that includes the full-length coding sequence of mouse, not human, $VEGF_{165}$ cDNA, and that is "driven by a tetracycline-responsive cytomegalovirus promoter and a vector encoding a transactivator protein that will activate VEGF expression only in the absence of tetracycline" (*see* Benjamin at p. 8761, Col. 2, last paragraph and p. 8762, Col. 1, 4th paragraph). Nowhere does Benjamin teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation that is regulated by the

untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with a composition comprising a cell free translation mixture and an mRNA transcript comprising a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the reporter gene coding sequence is not the coding sequence of human VEGF. Benjamin is focused on either turning on or off the production of VEGF protein in the cell using a tetracycline responsive promoter, with the intent of showing the effects of VEGF overproduction on tumor vasculature (*see* Benjamin at Abstract and p. 8764, Col. 1, 3rd paragraph). Nowhere does Benjamin teach or suggest use of human VEGF 5'UTR and 3'UTR and their regulation of VEGF translation, and as such the skilled artisan would not have reason or motivation to perform the claimed methods when faced with Benjamin alone.

Furthermore, nowhere does Benjamin teach or suggest a screening assay that involves contacting the compound with a second composition comprising a second cell-free extract and a second mRNA transcript, comprising the first reporter gene coding sequence operably linked to a second 5' UTR and a second 3' UTR, wherein the second 5' UTR is upstream of the first reporter gene coding sequence and the second 3' UTR is downstream of the first reporter gene coding sequence, and wherein the second 5' UTR and the second 3' UTR are each from a mRNA different than the 5' UTR and the 3' UTR of the human VEGF mRNA. There is nothing taught in Benjamin that would have prompted a person of ordinary skill in the art to develop methods for screening for candidate compounds that that modulates human VEGF mRNA translation that is regulated by the UTRs of the human VEGF mRNA, wherein the methods comprise contacting the compound with a second composition comprising a second cell-free extract and a second mRNA transcript comprising the 3' UTR and the 5' UTR of a *different* mRNA, as required by the claims, with a reasonable expectation of success.

As such the skilled artisan would not have arrived at the claimed invention when faced with Benjamin and Claffey. Accordingly, Benjamin, whether alone or in combination with Claffey, does not render obvious the claimed methods.

In view of the foregoing, Applicants submit that claim 53 is patentable over Claffey as applied to claims 44, 50-52, 54-56, 58, 59, 64 and 65, and further in view of Benjamin, and respectfully request that this rejection be withdrawn.

5. The Rejection over Claffey in view of Hyder and Cho

Claims 49 and 62-65 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Claffey, as applied to claims 45, 50-52 and 54-57, and further in view of Hyder *et al.*, 2000, Cancer Research, 60: 3183-3190 ("Hyder") and Cho *et al.*, 2002, Expert Opin Ther Targets, 6: 679-689 ("Cho"). Applicants respectfully disagree with the rejection of claims 49 and 62-65 for the reasons detailed below.

As discussed above, nowhere does Claffey teach or suggest a method for identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with either a cell engineered to express a reporter protein translated from a mRNA transcript or a composition comprising a cell-free translation mixture and a RNA transcript expressing a reporter protein translated from the RNA transcript, wherein the mRNA transcript comprises a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the 5' UTR is upstream of the reporter gene coding sequence and the 3' UTR is downstream of the reporter gene coding sequence, and wherein the reporter gene coding sequence is not the coding sequence of human VEGF. Moreover, since Claffey is only focused on examining the importance of the 3' UTR of human VEGF in increasing VEGF transcription and mRNA stability in response to hypoxia, Claffey provides no suggestion or reason to one of ordinary skill in the art to modify the luciferase-VEGF cDNA constructs of Claffey to include the full-length human VEGF 5' UTR, as required by the claims.

Hyder does not cure the deficiencies of Claffey. The focus of Hyder is to understand the molecular mechanism(s) underlying the induction of VEGF transcription in response to estrogen. In the investigation of such molecular mechanisms, Hyder identified eleven (11) short DNA sequences within the rat VEGF genomic sequence that have homology to a consensus estrogen response element, which has been shown to induce DNA transcription in response to estrogens (*see* Figure 1 of Hyder). Hyder demonstrates that two of the short DNA sequences, which were found in the 5' and 3' untranslated regions of the rat VEGF genomic sequence, specifically bind to human estrogen receptors in gel shift assays (*see, e.g.*, Hyder at Figures 2 and 3, and page 3185, Col. 1, 2nd full paragraph to page 3185, Col. 2, 1st

full paragraph). The fact that the two short DNA sequences with homology to a consensus estrogen response element were found in the 5' and 3' untranslated regions of rat VEGF would not have suggested to one of ordinary skill in the art that the mRNA transcribed from such DNA sequences would have any effect on expression. Rather, given the homology of such DNA sequences to a consensus estrogen response element, the specific binding of two of those DNA sequences to human estrogen receptors, and the known role of estrogen response elements in the induction of DNA transcription in response to estrogen, one of ordinary skill in the art would not have had any reason to use the described short DNA sequences for anything other than inducing rat VEGF transcription in the presence of estrogen.

In order to assess the transcriptional activities of the short DNA sequences with homology to a consensus estrogen response element, Hyder produced reporter constructs in which tandem copies of either the short DNA sequence within the 5' UTR of rat VEGF DNA or the 3' UTR of rat VEGF DNA, in either the endogenous or reverse orientation, were ligated upstream of a thymidine kinase promoter linked to a luciferase reporter. Hyder transfected such reporter constructs into HeLa cells along with plasmids encoding an estrogen receptor subtype and then the cells were incubated with or without estrogen (*see* Hyder at page 3185, Col. 2, last paragraph to page 3187, Col. 2, first paragraph and Figure 5). Luciferase activity was determined 24 hours after the incubation with or without estrogen (*see* Hyder at page 3187, Figure legend for Figure 5; Figure 5). Because of the role of the estrogen receptor in the induction of DNA transcription in response to estrogen, none of the reporter assays described in Hyder were performed without co-transfecting a plasmid encoding an estrogen receptor subtype into cells. In contrast, the claimed invention which recites methods for identifying a compound that modulates VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF would not have been suggested by an assay system that requires co-transfection of a plasmid encoding an estrogen receptor subtype. Moreover, the reporter assays that are described in Hyder do not suggest developing an assay system that comprises expressing a reporter protein translated from a mRNA transcript comprising a reporter gene coding sequence operably linked to both the full-length 5' UTR and full-length 3' UTR of the human VEGF mRNA, as required by the claims. On the contrary, the reporter constructs that were used in the reporter assays of Hyder contain tandem copies of the DNA sequences found in either the 5' or 3' UTR of genomic rat VEGF

which have homology to a consensus estrogen response element (cERE). The legend of Figure 1 in Hyder states "B, sequences of the VEGF regions (sense strand) homologous to the cERE." (*see* Hyder at Figure 1 legend at page 3184). In addition, the description of Figure 1 in the results section states that ".. . 11 sequences with a minimum 60% homology to the cERE .. . and [t]hese sequences are shown in Fig. 1B, and their location in the VEGF gene is indicated in Fig. 1A." (*see* Hyder at page 3185, 1st Col., 1st full paragraph).

There is no teaching or suggestion in Hyder to perform methods for identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, said method comprising contacting a compound with either a cell engineered to express a reporter protein translated from a mRNA transcript or a composition comprising a cell-free translation mixture and a RNA transcript expressing a reporter protein translated from the RNA transcript, wherein the mRNA transcript comprises a reporter gene coding sequence, operably linked to the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA, wherein the 5' UTR is upstream of the reporter gene coding sequence and the 3' UTR is downstream of the reporter gene coding sequence, and wherein the reporter gene coding sequence is not the coding sequence of human VEGF. Moreover, Hyder does not provide any reason that would have prompted a person of ordinary skill in the art to modify the transcription assays and reporters described in Hyder to perform a screening assay to identify compounds that modulate human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA using such reporter assays.

Further, nowhere does Hyder teach or suggest a screening assay that involves contacting the compound with a *second* human cell engineered to express a second reporter protein translated from a second RNA transcript comprising the *second* 3' UTR and the *second* 5' UTR of a mRNA different than human VEGF mRNA. There is nothing taught in Hyder that would have prompted a person of ordinary skill in the art to develop methods for screening for candidate compounds that modulate human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, comprising contacting a compound with a first human cell engineered to express a first reporter protein translated from a first RNA transcript comprising the first 3' UTR and the first 5' UTR of the human VEGF mRNA, and then contacting the compound with a second human cell engineered to express a second reporter protein translated from a second RNA transcript comprising the

second 3' UTR and the second 5' UTR of a different mRNA, wherein the reporter gene coding sequence is not the coding sequence of human VEGF, with a reasonable expectation of success. Further, given the known role of estrogen response elements for inducing DNA transcription in response to estrogen, one of ordinary skill in the art would not have had a reasonable expectation of successfully identifying a compound that modulates human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA using reporter constructs comprising the DNA estrogen-responsive sequences identified by Hyder. Accordingly, Hyder, whether alone or in combination with Claffey, does not render obvious the methods of claims 49 and 62-65.

Cho does not cure the deficiencies of Claffey or Hyder. Cho is a review article that discusses techniques for the identification of novel therapeutic targets for skeletal diseases (*see* Cho at abstract). Nowhere does Cho teach or suggest a screening assay for identifying compounds that modulate human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA, by performing reporter assays using a reporter protein translated from a mRNA transcript, wherein the reporter constructs encode both the full-length 5' UTR and the full-length 3' UTR of the human VEGF mRNA and wherein the reporter mRNA coding sequence is not the coding sequence of human VEGF. There is no teaching in Cho of VEGF, much less a teaching of a screening assay for identifying compounds that modulate human VEGF mRNA translation that is regulated by the untranslated regions of the human VEGF mRNA. Accordingly, Cho, whether alone or in combination with Claffey and Hyder, does not render obvious the methods of claims 49 and 62-65.

In view of the foregoing, Applicants submit that claims 49 and 62-65 are patentable over Claffey, as applied to claims 45, 50-52 and 54-57, and further in view of Hyder and Cho, and respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants believe that the present claims meet all the requirements for patentability. Consideration and entry of the foregoing amendments and remarks into the file of the application is respectfully requested. Withdrawal of all rejections and consideration of the amended claims are requested. If any issues remain, the Examiner is urged to telephone the undersigned.

Respectfully submitted,

Date: August 4, 2011

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